THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 16

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte HARRIET N. GLASSMAN,
DAVID C. JORDAN, HERBERT LEPOR
and ROBERT R. LUTHER

Appeal No. 1997-1842
Application 08/068,878

ON BRIEF

Before WINTERS, WILLIAM F. SMITH and LORIN, Administrative Patent Judges,

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1 through 7, all the claims remaining in the application. Claims 1, 2 and 7 are illustrative of the subject matter on appeal and read as follows:

1. A method for the chronic treatment for a period of at least two and one-half years of urinary symptoms associated with benign prostatic hyperplasia comprising administering to a male human patient in need of such treatment a therapeutically effective amount of 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]piperazine or a pharmaceutically acceptable salt thereof.

2. A method for the chronic treatment of urinary symptoms associated with benign prostatic hyperplasia comprising administering to a male human patient in need of such treatment a therapeutically-effective amount of 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)-carbonyl]piperazine monohydrochloride dihydrate.

7. The method of Claim 1 wherein said therapeutically effective amount of 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-tetrahydrofuroyl)piperazine or a pharmaceutically acceptable salt thereof is administered in the form of a soft elastic gelatin capsule formulation in unit dosage form comprising between 1 mg and 20 mg of active ingredient.

The references relied upon by the examiner are:

Lepor et al. (Lepor et al. 1988), “Laboratory Assessment of Terazosin and Alpha-1 Blockade in Prostatic Hyperplasia,” Urology, Supp. to Vol. 32 (6), pp. 21-26 (Dec. 1988).

Lepor, (Lepor 1989), “Role of Alpha-Adrenergic Blockers in the Treatment of Benign Prostatic Hyperplasia,” The Prostate, Supp. 3, pp. 75-84 (1990), Proc. of the Urological Assoc., Dallas, TX, May 6, 1989.

Lepor et al. (Lepor et al. 1989), “The Safety and Efficacy of Terazosin for the Treatment of Benign Prostatic Hyperplasia,” Int. J. Clin. Pharmacol. Ther. Toxicol., 27 (8), pp. 392-97 (Aug. 1989).

Dunzendorfer, “Effects of Terazosin in the Treatment of Benign Prostatic Hyperplasia,” Arzneimittelforschung, 39 (1), pp. 1289-91 (Oct. 1989).

Fabricius et al. (Fabricius), “Efficacy of Once-A-Day Terazosin in Benign Prostatic Hyperplasia: A Randomized, Double-Blind Placebo-Controlled Clinical Trial,” The Prostate, Supp. 3, pp. 85-93 (1990).

Lepor et al. (Lepor 1992), "The Safety, Efficacy and Compliance of Terazosin Therapy for Benign Prostatic Hyperplasia," J. Urology, 147, pp. 1554-57 (June 1992).

The references relied upon by this merits panel are set forth above and the following:

"HYTRIN®," in Physicians' Desk Reference®, 526-28 (45th ed., New Jersey, publisher Edward R. Barnhart, 1991).

Roteman	4,251,532	Feb. 17, 1981
Kyncl et al. (Kyncl)	5,212,176	May 18, 1993 (filed June 29, 1990)

Claims 1-7 stand rejected under 35 U.S.C. § 103. The examiner relies upon Lepor et al. 1988, Lepor et al. 1989, Lepor et al. 1992, Lepor 1989, Dunzendorfer and Fabricius as evidence of obviousness. We vacate the examiner's rejection and enter a new ground of rejection under the provisions of 37 CFR § 1.196(b).

DISCUSSION

Claim 1 and claims which depend from claim 1 are directed to a method for the chronic treatment, for a period of at least two and one-half years, of urinary symptoms associated with benign prostatic hyperplasia (BPH). The method comprises the step of administering to a male human patient in need of such treatment a therapeutically effective amount of 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]piperazine or a pharmaceutically-acceptable salt thereof.

Claim 2 and claims which depend from claim 2 are directed to the method recited in claim 1, but 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]piperazine monohydrochloride dihydrate is administered as the active ingredient.

According to the present specification, the compound recited in claim 1, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]piperazine is also known as "terazosin." Specification, page 1, lines 6-7.

The examiner states that claims 1 through 7 are rejected under 35 U.S.C. § 103 as being unpatentable over Lepor et al. 1988, Lepor et al. 1989 and Lepor 1992, Lepor 1989, Dunzendorfer or Fabricius. See the Answer, pages 2 and 3. The examiner "describes" each reference in a single brief sentence followed by three additional short quotes from Lepor 1989. The examiner concludes, "[i]n view of this, one skilled in the art would be motivated to treat symptomatic BPH with terazosin indefinitely at 10 mg per dose." In reviewing the examiner's position, we are unable to discern precisely to what "this" refers, e.g., Lepor 1989, or one of the other five references.

The examiner's rejection is difficult to review since it is not clear whether the examiner relies on the combination of all six references, on each of the six references individually, or on some other combination thereof, such as those proposed by appellants. See the Brief, pages 2 and 3.

Furthermore, the rejection is difficult to review since the examiner has failed to state how one of ordinary skill in the art would have found the subject matter of any claim on appeal as a whole obvious. Rather, we only have two statements from the examiner as to what one of ordinary skill in the art purportedly would have been "motivated" to do. We remind the examiner that the statutory standard under 35 U.S.C. § 103 is one of obviousness, not motivation. The word "motivation" is normally used in the context of determining obviousness under section 103 when it becomes necessary to combine reference disclosures as evidence that one of ordinary skill in the art would have found the subject matter of a claim as a whole obvious within the meaning of the statute. See, e.g., Pro-Mold and Tool Co. v. Great Lakes Plastics Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996) ("It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references.")

Our review of this case leads us to conclude that there is evidence of record which renders the claims on appeal unpatentable under 35 U.S.C. § 103. Rather than spend the resources of the Board in an attempt to guess what was on the examiner's mind in making the rejection, we vacate the rejection and enter the following new ground of rejection.

NEW GROUND OF REJECTION UNDER 37 CFR § 1.196(b)

We initially note that there is a need to resolve confusion concerning the scope of claim 2 on appeal. The examiner stated on page 4 of the Examiner's Answer that claim 2 does not require that the treatment be for a period of at least two and one-half years. We disagree.

The term "chronic treatment" recited in claims 2, 4 and 6 is defined in the specification as "continuing, on-going treatment for the duration of urinary symptoms associated with benign prostatic hyperplasia and means a period of treatment of at least two and one-half years" (emphasis added). Specification, page 3, lines 26-29. Thus, the chronic treatment required by claim 2 must be for a period of at least two and one-half years.

I. Claims 1 through 6 are rejected under 35 U.S.C. § 103(a). As evidence of obviousness, we rely upon Lepor et al. 1988, Lepor et al. 1989, Lepor 1992, Fabricius, Dunzendorfer and HYTRIN®.

The following findings of fact are supported by substantial evidence in the record as noted.

1. The administration of terazosin in the treatment of urinary symptoms associated with benign prostatic hyperplasia (BPH) is well-known in the art, as shown by Lepor et al. 1989, Lepor 1992, Dunzendorfer and Fabricius.

2. BPH is a condition of benign enlargement of the prostate gland that occurs in the aging male. Fabricius, page 92, lines 8 and 9.

3. Clinically, BPH manifests as bladder obstruction. A prostate adenoma (benign tumor of glandular origin) obstructs urinary flow by static and dynamic components. Static, or mechanical obstruction is caused by the enlarged prostate itself. The dynamic component of the prostate obstruction presumably is related to the tone of the prostate smooth muscle. Lepor et al. 1989, page 392, column 1, lines 2-10.

4. Surgical removal of the prostate adenoma has been the main treatment of BPH. Fabricius, page 92, lines 9-10.

5. Transurethral resection and transurethral incision of the prostate have also been used in the treatment of BPH. In a long-term study, it was shown that the initial increase in peak urinary flow rate observed after transurethral resection and transurethral incision of the prostate decreased by approximately 20% and during the three-year follow-up, whereas the improvements in obstructive and irritative symptom scores were maintained. After three years, the peak urinary flow rate was only 51% and 12% greater than baseline values, respectively. Lepor 1992, page 1556, column 2, lines 16-25.

6. The tone of the prostate smooth muscle is dependent on the degree of activation of the α-adrenoceptors. These adrenoceptors have been shown to be

predominately α_1. Dunzendorfer, page 1289, column 1, lines 13-16. Lepor et al. 1988, page 26, lines 5-7.

7. Several clinical trials in Europe have demonstrated that alpha-adrenergic blockers are safe and effective for the treatment of symptomatic BPH. The efficacy of alpha-blockers was usually based upon improvement in urinary flow rates and reduction in urinary frequency. Lepor et al. 1989, page 392, column 2, first paragraph.

8. Lepor et al. 1988 demonstrated that terazosin, a well-known hypertension medication, is a very selective α_1- adrenergic blocker in the human prostate. Lepor et al. 1988, page 25, column 1, third full paragraph, and Figure 4.

9. Dunzendorfer discloses that terazosin has been shown to be safe and effective given once a day in the treatment of patients with mild to moderate hypertension. Dunzendorfer, page 1289, column 2, lines 11-14.

10. Lepor et al. 1989 discloses that the primary advantage of terazosin (HYTRIN®[1]) over other available alpha-adrenergic blockers, such as prazosin, is that its longer half-life allows for a once-daily dose. Lepor et al. 1989, page 393, column 1, lines 2-7.

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[1]The compound sold under the trademark HYTRIN® is identified as terazosin hydrochloride, i.e., 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]-piperazine, monohydrochloride, dihydrate. See HYTRIN®. This is the compound recited in claims 2, 4 and 6.

11. Lepor et al. 1989 reported the results of a two-month dose-titration study of terazosin in the treatment of BPH. Twenty-two normotensive patients with moderate symptoms of BPH were initially given 1 mg/day of terazosin (HYTRIN®). The dose was subsequently increased to 5 mg/day over an interval of one month. The 5 mg/day dose was continued for another month. Twenty-two patients continued the two month study. The remainder of the patients did not complete the study because of adverse drug reactions and poor compliance. Page, 393, column 1, lines 2, 13, 14, 38-49; page 393, column 2, lines 23-31.

12. Lepor et al. 1989 showed that after two months, the peak and mean urinary flow rates increased 63% and 61%, respectively, and the mean obstructive and irritative symptom scores deceased 62% and 33%, respectively. Lepor et al. 1989 disclosed that the observed changes from the baseline urinary flow rates and symptom scores were statistically and clinically significant. Page 393, column 2, lines 32-38; and Table 5.

13. Lepor et al. 1989 disclosed that terazosin was well tolerated in the normotensive patients, and that adverse drug reactions were all mild and readily reversible. Page 393, column 2, lines 46-49; page 396, column 1, lines 39-41; and Table 7.

14. Lepor et al. 1989 concluded that their study indicated that terazosin is safe and effective for the treatment of symptomatic BPH. Page 396, column 2, lines 9-13.

15. Lepor 1992 reported the results of a two-year clinical trial of terazosin for the treatment of symptomatic BPH. Forty-five normotensive patients with symptomatic BPH were initially given 1 mg/day of terazosin. The dose was subsequently increased to 5 mg/day over an interval of one month. The patients were maintained on 5 mg of terazosin throughout the remainder of the study. Twenty-one patients continued the two year study. The remainder of the patients were excluded because of adverse drug reactions, slight or no clinical response, deterioration of clinical response, lack of compliance, etc. Page 1554, column 1, second paragraph, through page 1555, column 3, line 31.

16. Lepor 1992 reported that the obstructive and irritative symptom scores decreased by 63% and 65%, respectively, after two months of terazosin therapy. The improvements in obstructive and irritative symptom scores were maintained throughout the two-year follow-up. The peak and mean urinary flow rates improved by 42% and 48%, respectively, after two months of terazosin therapy. The changes in mean urinary flow rate increased, whereas the changes in peak urinary flow rate decreased during the follow-up. Page 1555, column 1, first and second paragraphs; page 1556, column 2, lines 1-15; Figures 1 and 2.

17. Lepor 1992 disclosed that their study underestimates the efficacy of terazosin since a maximal therapeutic dose was not administered. Lepor 1992 disclosed that a randomized placebo-controlled study, not yet published, compared a

placebo, and 2, 5 and 10mg terazosin. The dose response data in that study indicated that the clinical response to terazosin may not reach a plateau even at 10 mg. Page 1556, column 2, lines 25-35.

18. Lepor 1992 concluded that their study demonstrated the safety, efficacy and compliance of terazosin therapy for BPH during a two-year follow-up. Page 1556, column 2, first full paragraph.

19. Dunzendorfer reported the results of a six-month clinical study of the use of terazosin for the treatment of symptomatic BPH. Fifteen patients with diagnosed BPH participated in the study. The study was divided into two parts: (1) a four-week, single-blind, placebo lead-in period, and (2) a six-month, single-blind treatment period. At the first and second lead-in visits, patients were given a placebo. At the final visit of the placebo lead-in period, each patient received an initial daily dose of 1 mg terazosin for the first two weeks of the treatment period. The daily dosage was increased sequentially at subsequent two week intervals to 2, 5 and 10 mg until there was a therapeutic response to treatment at a particular dose or until maximum daily dosage of 10 mg terazosin was reached. Patients were then maintained at that dose for the remainder of the study. Page 1290, column 1, section 2.3.

20. Dunzendorfer reported that the obstructive and irritative symptom scores decreased by 55% and 24%, respectively, after six months of terazosin therapy. The

peak and mean urinary flow rates improved by 49% and 36%, respectively. Page 1290, column 1, last paragraph, through the column 2, second paragraph.

21. Dunzendorfer concluded that terazosin taken once-a-day offers benefits in treating the symptoms of patients with BPH. Page 1291, column 1, third paragraph.

22. None of the references explicitly describe the administration of terazosin in the treatment of BPH for a period of at least two and one-half years.

23. Fabricius shows that when BPH patients taking terazosin stop taking terazosin, the beneficial effects of terazosin in the relief of symptoms of BPH were not sustained.

24. Fabricius reported the results of a randomized, placebo-controlled, double-blind study, where 10 mg/day of terazosin was given to fifty-seven patients with BPH. After a four-week placebo lead-in and a 24-week treatment period (the single-blind phase) with terazosin, thirty patients who responded to terazosin were randomly assigned either to be given terazosin or a placebo for twelve weeks (double-blind phase). Fabricius, page 86, line 14, to page 87, line 6.

25. During the single-blind treatment period, the peak urine flow rate increased 54%, after terazosin treatment. The mean flow rate increased 55%. The mean obstructive symptom score and irritative symptom source improved 68% and 34%, respectively. Fabricius, Table 1, and the accompanying text.

26. During the double-blind period, the improvement in all the variables was sustained in the terazosin group but not in the placebo group. In the placebo group, all the variables reverted back to baseline values (before treatment with terazosin) at the end of the double-blind period. Fabricius, page 88, first full paragraph, Figures 1 through 5.

27. Fabricius concluded that terazosin had been shown to be effective and safe in relieving the symptoms of BPH. In particular, terazosin was shown to be effective in increasing urine flow rates and decreasing residual urine volume when administered once a day. Fabricius, page 92, last paragraph.

We conclude, on the basis of findings 11, 12, 15, 16, 19, 20, 24 and 25, that the treatment period of terazosin is a result-effective variable, and variation of the period of treatment would be well within the skill of the ordinary worker in the art. See In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980).

Based on finding 26, the person having ordinary skill in the art would have readily understood that it is desirable to continue treating patients with symptomatic BPH with terazosin for as long as the symptoms persist. As illustrated in finding 5, without the surgical removal of the prostate adenoma, the urinary symptoms of BPH persist for at least three years. On the other hand, findings 24-26 establish that halting terazosin treatment results in the reoccurrence of the urinary symptoms of BPH. Thus, the prior art provides a strong reason, suggestion or motivation to maintain terazosin treatment.

Accordingly, we hold that the daily administration of terazosin, such as HYTRIN®, to patients with symptomatic BPH, in amounts of 5 to 10 mg, which are within the scope of claims 1-6, for as long as the symptoms persist, would have been obvious to the person having ordinary skill in the art. As discussed above, without the surgical removal of the prostate adenoma, it is reasonable to expect that the urinary symptoms of BPH will persist for at least three years. Thus, the prior art suggests the claimed treatment for a period of at least two and one-half years.

II. Claim 7 is rejected under 35 U.S.C. § 103(a). As evidence of obviousness, we rely on Lepor et al. 1988, Lepor et al. 1989, Lepor 1992, Fabricius, Dunzendorfer and HYTRIN®, as applied to claim 1 above, and additionally on Roteman and Kyncl.

We have held above that the disclosures of Lepor et al. 1988, Lepor et al. 1989, Lepor 1992, Fabricius, Dunzendorfer and HYTRIN® would have rendered obvious the chronic treatment of urinary symptoms associated with BPH by daily administering terazosin as required by claims 1-6 on appeal. However, none of the references describe terazosin in the form of a soft elastic gelatin capsule formulation as required in claim 7. In this regard we point out the product sold under the trademark HYTRIN® is in the form of a tablet.

Roteman discloses that terazosin hydrochloride dihydrate, which is the active agent in the composition sold under the trademark HYTRIN®, can be administered in the form of tablets or capsules. Roteman, col. 5, line 31.

Kyncl discloses that the R(+)enantiomer of terazosin hydrochloride dihydrate can be used in the treatment of diseases characterized by abnormally high levels of α_1-adrenergic activity, which include BPH. Column 2, lines 62-66. Kyncl discloses that said active ingredient can be administered as a soft-filled gelatin capsule or as a tablet. Column 7, lines 17-18, 25 and 38-42.

In view of the additional teachings of Roteman and Kyncl, we hold that the administration of terazosin in the form of a soft-filled gelatin capsule in the chromic treatment of patients having symptomatic BPH would have been obvious to one of ordinary skill in the art .

TIME PERIOD FOR RESPONSE

This opinion contains a new ground of rejection pursuant to 37 CFR § 1.196(b) (amended effective Dec. 1, 1997, by final rule notice, 62 Fed. Reg. 53,131, 53,197 (Oct. 10, 1997), 1203 Off. Gaz. Pat. & Trademark Office 63, 122 (Oct. 21, 1997)). 37 CFR § 1.196(b) provides that, "A new ground of rejection shall not be considered final for purposes of judicial review."

37 CFR § 1.196(b) also provides that the appellants, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options

with respect to the new ground of rejection to avoid termination of proceedings (§ 1.197(c)) as to the rejected claims:

> (1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner. . . .
>
> (2) Request that the application be reheard under § 1.197(b) by the Board of Patent Appeals and Interferences upon the same record. . . .

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

VACATED; 37 CFR § 1.196(b)

Sherman D. Winters Administrative Patent Judge	)
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